Synthesis of 2-Isopropylidenehydrazinylthiazole and its Subsequent Annelation to the Corresponding Thiazolo[2,3-*c*]-*s*-triazole

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An unequivocal synthesis of a new thiazolo[2,3-*c*]-*s*-triazole substituted at the C-5 position by a very useful methyl triphenylphosphonium salt has been achieved starting from the corresponding 2-isopropylidenehydrazinylthiazole and formic acid. Ring closure was found to be very easy without isolation of a formylhydrazino intermediate. The thiazole derivative was prepared from isopropylidenethiosemicarbazide and (3-chloro-2-oxo)propyltriphenylphosphonium chloride in a good yield.

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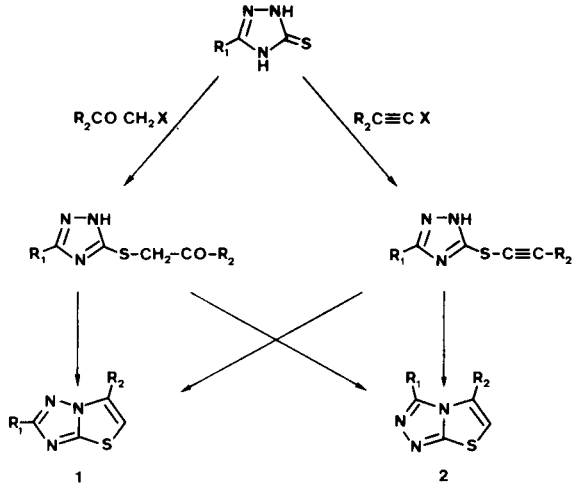
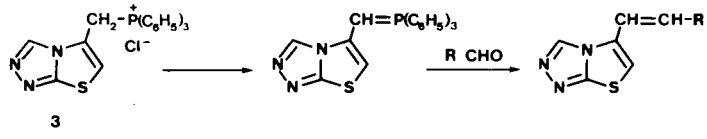
In recent years, an increasingly large number of pharmacologically active agents have been investigated which contain a bicyclic fused [5,5] ring system. Among this class of compounds, 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]-*s*-triazole and related substances have been the subject of intense interest, more particularly in the field of cancer chemotherapy [1,2,3]. In connection with our recent studies on potential antitumor fused [4-8] or not condensed [9,10] heteroaromatic rings, we wish to describe in this report the synthesis of a new thiazolo[1,2,4]triazole, also containing a thiazole ring and a bridgehead nitrogen.

The recognized paths used to prepare the thiazolo-[1,2,4]triazole ring involve either the reaction of *s*-triazole-3-thiol with α-haloketones [11-15] or propargyl bromide [14,16-18]. However, intramolecular cyclization of these intermediates led to thiazolo[3,2-*b*]-*s*-triazole **1** and/or to the isomeric thiazolo[2,3-*c*]-*s*-triazole **2** (Scheme 1). The cyclization pathways appear to be influenced by the acidity of



SCHEME 1

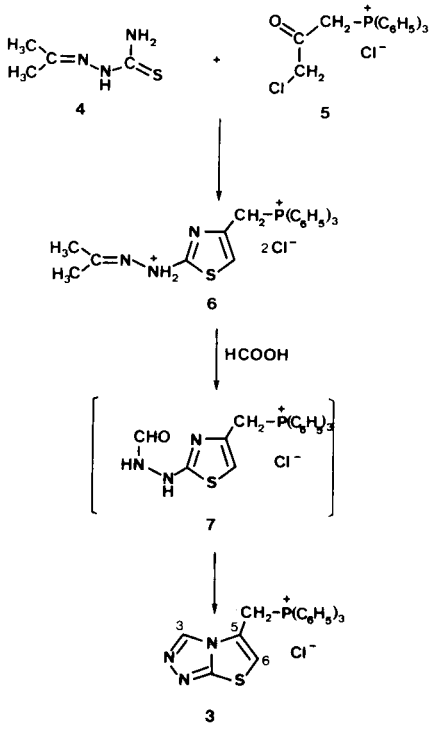


SCHEME 2

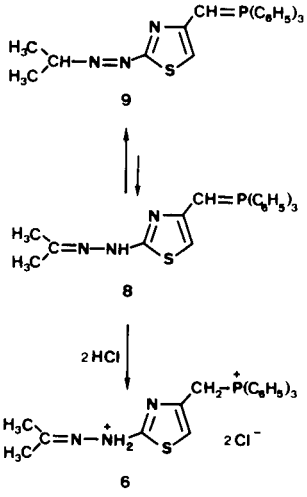
the medium, the solvent polarity and the temperature which alter the basicity of the nitrogen atoms. The effect of the experimental conditions and of the nature of the substituent R_1 have been largely studied [12,15,19,20]. Unequivocal synthesis of thiazolo[3,2-*b*]-*s*-triazole **1** has been achieved starting from the appropriate thiazole ring. Thus, 2-imino-3-aminothiazolines [21,22] or 3-amino-2-formamidothiazolium salts [23,24] readily gave the bicyclic fused ring system **1**. On the other hand, thiazolyl-2-hydrazide unambiguously underwent a dehydrative cyclization to thiazolo[2,3-*c*]-*s*-triazole **2** [12,15]. In fact, the synthesis thus far reported involved thiazolo[2,3-*c*]triazoles substituted by only simple aryl or alkyl moieties. We have investigated this synthetic approach to ring system **2** but we have prepared a new bicyclic heteroaromatic compound **3** with a very efficient functional group at C-5 position, precisely a potent phosphorane ylide Wittig reagent for the synthesis of conjugated olefines (Scheme 2). Such fused polycyclic heteroaromatic compounds conjugated with double bonds could exhibit an interaction with DNA inducing either carcinogenic or antitumor effects [25].

The synthesis of **3** is outlined in Scheme 3. First cyclization to thiazole **6** has been carried out from thiosemicarbazone **4** and phosphonium salt **5** in almost quantitative yield. This starting material **5** has been easily obtained by action of triphenylphosphine on dichloroacetone in equimolecular proportions [26]. The utility of such a polyfunctionalized compound as a useful synthon is well established: the chloromethylketone group may be involved in a number of heterocyclizations and the methyl phospho-

nium salt readily used as a Wittig reagent. The spatial structure has been achieved in order to visualize the relative positions of the three functional groups [26].



SCHEME 3



SCHEME 4

Thiazole ring closure actually occurred in a very high yield without a cyclizing agent and **6** was isolated as a bi-salt (monophosphonium chloride and monohydrochloride). In order to determine which nitrogen was protonated, we compare the ^{1}H nmr spectra of **6** and of the corresponding base **8** (the phosphonium group was thereby converted to the phosphorus ylide). The signal attributed to the protons of the methyl groups appeared as a singlet for **6** and as a doublet for **8**. A tautomerism involving the forms **8** and **9** (Scheme 4) could account for this assignment. The tautomeric structure **9** in which the methyl groups are coupled with the proton attached to the C atom could explain the presence of a doublet at 1.85 ppm (J = 3 Hz) and the structure **8**, more favoured in acidic medium could lead to the hydrochloride **6** in which the methyl groups are equivalent.

It is surprising that cyclization to thiazolotriazole **2** had occurred starting with the hydrochloride **6** and formic acid in a one-step reaction. The intermediate **7** was not isolated in such conditions and only the expected product **3** was obtained in a good yield.

Structure was established by elemental analysis and nmr spectrum and indicated the presence of two molecules of water of crystallization. On the nmr spectrum, the methylene group appeared as a doublet ($J_{P,H}$ = 16 Hz) and the nucleus protons H_3 and H_6 as singlets at 8.64 and 6.62 ppm respectively (see **3**, Scheme 3).

EXPERIMENTAL

Melting points were determined in capillary tubes and were uncorrected. The ir spectra were recorded on a Perkin Elmer 177 in potassium bromide pellets. The nmr spectra were obtained from a Jeol JNM-MH-60 apparatus. The chemical shifts are in ppm using tetramethylsilane as internal standard. Microanalyses were performed in part with a Perkin Elmer CHN 240 and for Cl, P, O and S determinations by the "Service Central de Microanalyses du CNRS, Vernaison, France".

1-Isopropylidenethiosemicarbazide (**4**).

Isopropylidenethiosemicarbazide (**4**) was prepared as previously described [27] in a 70% yield, mp 180°; ir: 3370, 3210, 3150 cm^{-1} (NH, NH_2); ^{1}H nmr (DMSO-d_6): δ 1.95 (s, 6H, methyl), 7.52 (s, 1H), 7.97 (s, 1H) and 9.90 (s, 1H), three protons exchangeable by deuterium oxide and corresponding to the structure -NH-C(=NH)-SH.

(3-Chloro-2-oxo)propyltriphenylphosphonium Chloride, Monohydrate (**5**).

A solution of 26.2 g (0.1 mole) of triphenylphosphine and 12.7 g (0.1 mole) of 1,3-dichloroacetone in benzene was stirred under reflux for 2 hours. The precipitated product was crystallized from ethanol-water (4/1) to give **5** in 87% yield, mp 173-174°; ir: 1735 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 7.82 (m, 15H, phenyl protons), 6.20 (d, 2H, phosphomethylene protons, $J_{P,H}$ = 12 Hz), 5.00 (s, 2H, water), 4.15 (s, 2H, chloromethylene protons).

Anal. Calcd. for $C_{21}H_{19}Cl_2OP \cdot H_2O$: C, 61.92; H, 5.16; Cl, 17.44; O, 7.86; P, 7.62. Found: C, 62.04; H, 5.24; Cl, 17.49; O, 7.92; P, 7.59.

[2-(2-Isopropylidenehydrazinyl)-4-methylenethiazolyl]triphenylphosphonium Chloride Hydrochloride (**6**) and 2-(2-Isopropylidenehydrazinyl)-4-methynethiazolyl-triphenylphosphorane (**8**).

A solution of isopropylidenethiosemicarbazide (**4**) (5.24 g, 0.04 mole) and phosphonium salt **5** (16.24 g, 0.04 mole) in ethanol (200 ml) was stirred and heated under reflux for 24 hours. The reaction mixture was evaporated to dryness and the residue triturated in ethyl acetate to give 93% of product. An analytically pure sample was obtained by recrystallization from ethyl acetate, mp 190-192°; ir: 2950, 2450 (NH_2^+), 1600 cm^{-1} (C=N); ^{1}H nmr (DMSO-d_6): δ 7.82 (m, 15H, phenyl protons), 6.50 (s, 1H, CH-5 thiazole), 5.15 (d, 2H, phosphomethylene, $J_{P,H}$ = 15 Hz), 4.50 (s, 2H, NH_2^+), 1.90 (s, d after exchange by deuterium oxide, 6H, CH_3).

An aqueous solution of sodium hydroxide (0.1 *N*) was added to an aqueous solution of **6** up to basic *p*H. Pale yellow crystals formed, mp 232-235°; ir: 1620 cm^{-1} (C=N); ^1H nmr (DMSO-d_6): δ 7.70 (m, 15H, phenyl protons and 1H, methylidene), 4.20 (s, 1H, CH-5 thiazole), 4.05 (m, 1H, CH isopropyl), 1.85 (d, 6H, CH_3, $J_{CH,CH3}$ = 3 Hz).

Anal. Calcd. for $C_{25}H_{24}N_3PS$: C, 69.90; H, 5.63; N, 9.78; P, 7.22; S, 7.46. Found: C, 69.45; H, 5.75; N, 9.61; P, 7.34; S, 7.50.

[(Thiazolo[2,3-*c*]triazolyl)-5-methylene]triphenylphosphonium Chloride (**3**).

A mixture of compound **6** (5.01 g, 0.01 mole) with 20 ml of formic acid was heated under reflux for 12 hours. The excess of formic acid was removed under reduced pressure and the solid residue was recrystallized from ethanol, mp 74-75°; ^1H nmr (DMSO-d_6): δ 8.64 (s, 1H, CH-3), 7.75 (s, 15H, phenyl protons), 6.62 (s, 1H, CH-6), 5.16 (d, 2H, methylene, $J_{P,H}$ = 16 Hz), 3.80 (s, 4H, water).

Anal. Calcd. for $C_{23}H_{19}N_3ClPS\cdot 2H_2O$: C, 58.53; H, 4.91; N, 8.90; O, 6.78; Cl, 7.51; P, 6.57; S, 6.79. Found: C, 58.43; H, 4.94; N, 8.94; O, 6.66; Cl, 7.60; P, 6.43; S, 6.80.

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